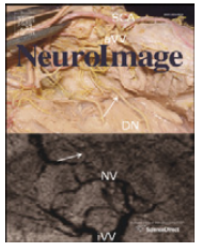
NeuroImage 61 (2012) 56–61

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg



A clustering-based method to detect functional connectivity differences

Gang Chen [a], B. Douglas Ward [a], Chunming Xie [a], Wenjun Li [a], Guangyu Chen [a], Joseph S. Goveas [b], Piero G. Antuono [c], Shi-Jiang Li [a,b,*]

[a] Department of Biophysics, Medical College of Wisconsin, Milwaukee, WI, USA
[b] Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI, USA
[c] Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

ARTICLE INFO

Article history:
Accepted 18 February 2012
Available online 3 March 2012

Josu Maiora

1. Introduction

- Recently, resting-state functional magnetic resonance imaging **(R-fMRI)** has emerged as a **powerful tool** for investigating normal human brain functional organization.

- Extracting valuable information hidden in the gigabytes of four dimensional images of hundreds to thousands of subjects remains a **challenge.**

- Preprocessing (numerous studies) <> **Postprocessing (challenging)**

- If a normal IC (Independent component) or cluster has **disappeared** in the diseased group because of the effect of the disease, it is possible that this IC or cluster will **not be identified** using the combined data.

- A new clustering-based method that clearly defines the clusters to quantify the functional connectivity differences →only **one set of clusters** for the entire cohort.

2. Materials and methods: subjects

Seventeen amnestic mild cognitively impaired (aMCI) and 22 cognitively normal (CN) subjects
(Memory Disorders Clinic at the Medical College of Wisconsin)

2. Materials and methods: Image acquisition

- Imaging was performed using a whole-body 3 T Signa GE scanner

- During the resting-state acquisitions, no specific cognitive tasks were performed, and the study participants were instructed to close their eyes and relax inside the scanner.

2. Materials and methods: Data preprocessing

- A series of preprocessing steps common to most fMRI analysis was conducted, using
  - Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov/afni/),
  - SPM8 (Wellcome Trust, London, UK) and
  - Matlab
- The preprocessing allows for
  - T1-equilibration (removal of the first five volumes of fMRI data).
  - cardiac and respiratory artifacts
  - slice-acquisition-dependent time shift correction (3dTshift);
  - motion correction (3dvolreg);
  - detrending (3dDetrend);
  - despiking (3dDespike);
  - Segmentation (SPM8) of white matter and CSF components
  - …

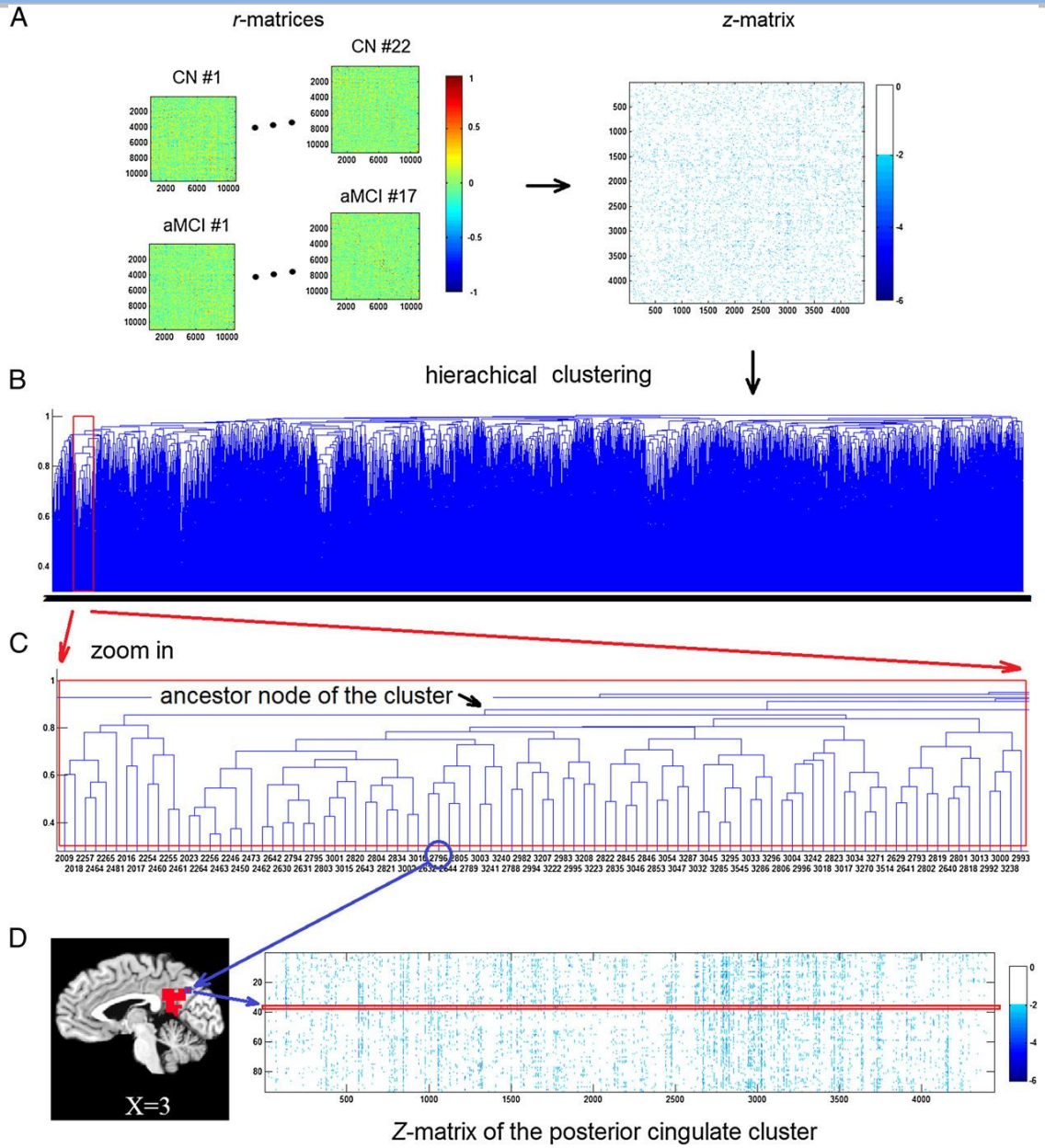
2. Materials and methods: Group difference information guided clustering method

- Functional connectivity difference information between the aMCI and CN groups was used to produce voxelwise clusters using Pearson product-moment correlation coefficient (r).
- The Fisher transformation $m=0.5\ln[(1+r)/(1-r)]$, which yielded variants of approximately normal distribution, was applied to the individual r-matrix to generate the m-matrix.
- A one-tailed two-sample t-test was conducted to examine whether m_{ij} of the aMCI group was significantly less than that of the CN group.

2. Materials and methods: Group difference information guided clustering method

- The one-tailed test was employed because we only considered the **reduced connectivity** in this study to demonstrate the method.
- The p-values were transformed to **Z-values**, using the inverse of the normal cumulative distribution function.
- The Z-value was then **thresholded** at $Z < -1.96$
- To reduce computation cost and the chance of false discovery, voxels with reduced connectivity to **less than 275 voxels** were removed.
- As a result, 4442 voxels were retained. The retained thresholded Z-matrix is shown in Fig. 1A (right).

2. Materials and methods: Group difference information guided clustering method



2. Materials and methods: Group difference information guided clustering method

- The hierarchical relationship of the 4442 voxels (Fig. 1B) was obtained based on the similarity of their Z-vectors. The clustering analysis was implemented, using the functions “linkage” and “dendrogram” in the MATLAB Statistics Toolbox.

- The “correlation” method was used in the “linkage” function to calculate the distance (d) between voxels. Specifically,

  $d_{ij} = 1 - r_{ij}$

  where, rij is the correlation coefficient between the Z-vectors belonging to voxel i and voxel j.

2. Materials and methods: Group difference information guided clustering method

- Each level of the hierarchy represents a particular grouping of the voxels into a unique cluster (Fig. 1C).

- To determine the functional homogeneity of a cluster, a **homogeneity index** was defined:

  homogeneity index = min (r_i, i∈voxels in the cluster)

  where ri is the correlation coefficient between voxel i's Z-vector and the cluster's Z-vector.

2. Materials and methods: Group difference information guided clustering method

- To obtain the **cluster size thresholds**, a subject permutation test was performed.

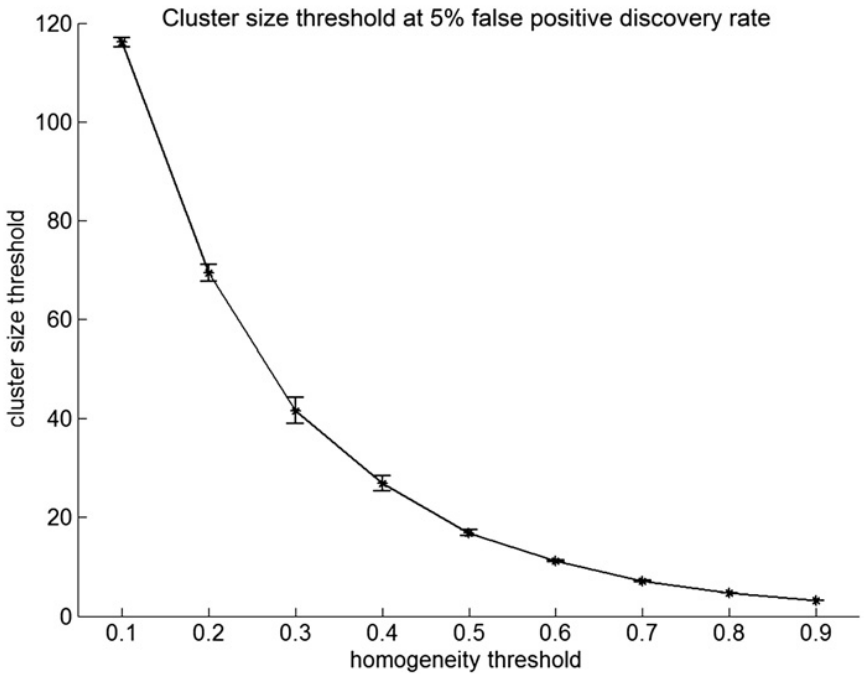
- The individual cluster size threshold was set so that there was less than a 4.7% chance (uncorrected) to identify a cluster that satisfied all of the following conditions in randomly grouped subjects:
  1. the voxels in the cluster were all spatially connected;
  2. the number of voxels in the cluster was more than the cluster size threshold;
  3. the homogeneity index of the cluster was above the corresponding homogeneity threshold.

2. Materials and methods: Connectivity index

- A connectivity index was defined to quantify the **decreased connections** in each subject.
- To avoid double-dipping or bias from circularity, we performed the **leave-one-out** procedure.
- The thresholded cluster Z-matrices were used to create decreased functional connectivity masks for all Z-values < −1.96 ($p < 0.025$).
- Then, all m-values in the masks of the excluded subject, were averaged. The **averaged m-value** was defined as the subject's **connectivity index**.

3. Results

- The curve was used to determine spatially connected clusters with both larger cluster size and higher homogeneity index than the values on the curve.



3. Results

- Based on the false-positive discovery rate curve in Fig. 2 and the functional connectivity difference information between aMCI and CN groups**, three clusters** above the curve were identified, as demonstrated in Fig. 3.

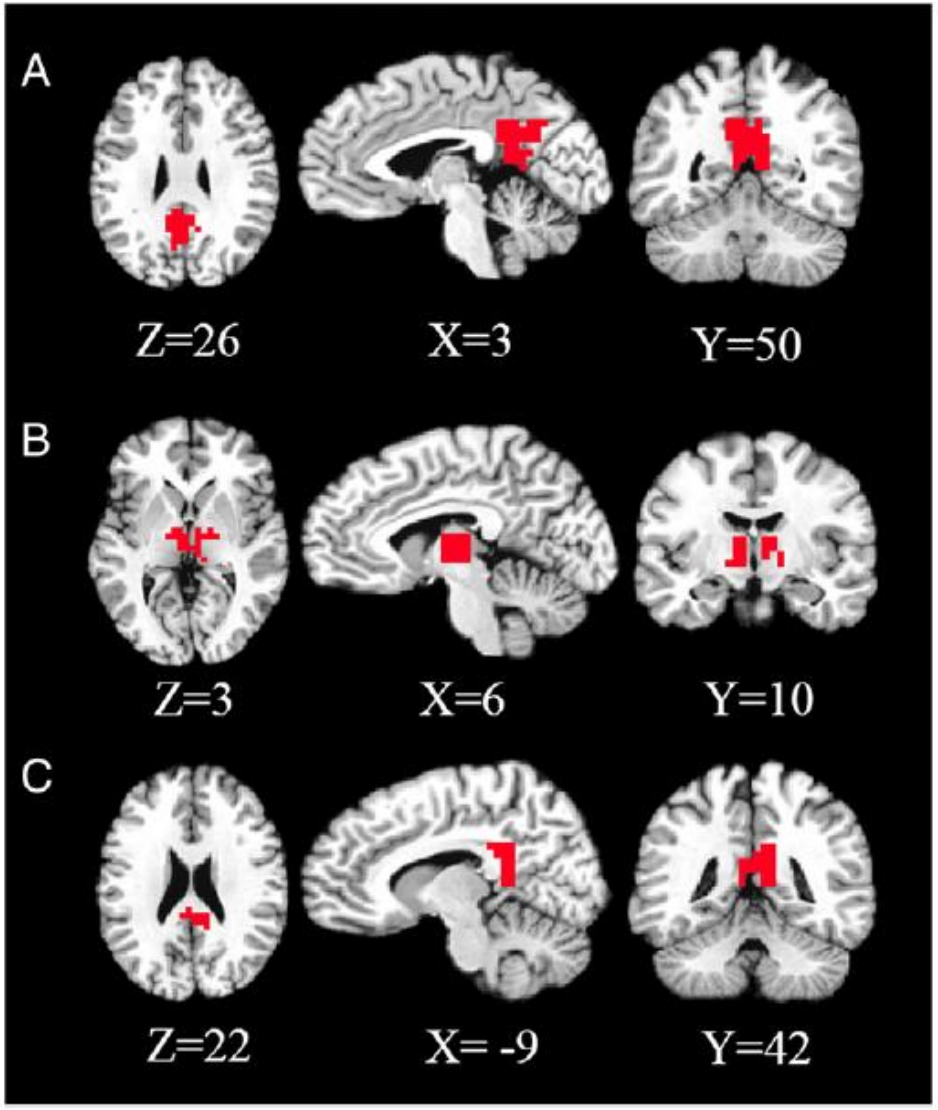


Fig. 3. The clustering method identified three clusters, using group difference information. (A) The posterior cingulate cluster. (B) The thalamus cluster. (C) The retrosplenial cingulate cluster.

3. Results

- Fig. 4 shows the decreased connectivity patterns for each of the three clusters. The color bar indicates the disconnection percentage.
- For example, light blue indicates that a voxel is disconnected from a corresponding cluster by 75% to 100%.
- The percentage was obtained by the number of voxels whose Z-values were less than −1.96, divided by the total number of voxels in the cluster

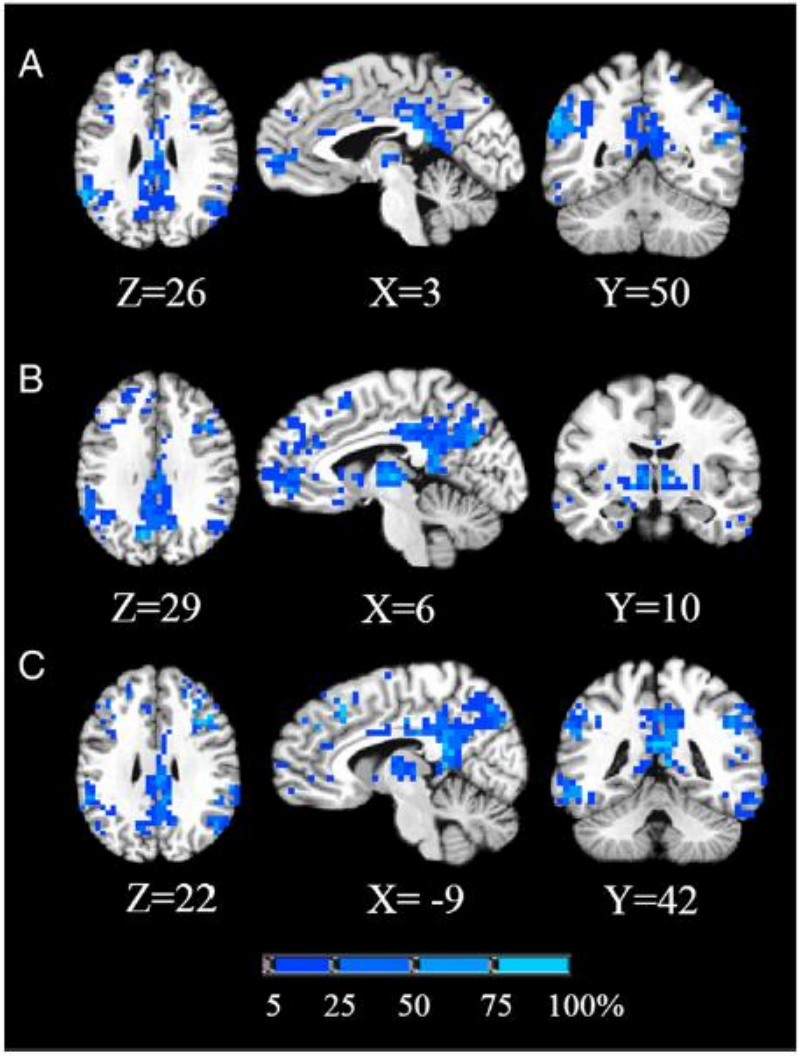


Fig. 4. Decreased connectivity to the three clusters shown in Fig. 3. (A) The posterior cingulate cluster. (B) The thalamus cluster. (C) The retrosplenial cingulate cluster. Color bar indicates the percentage of disconnection. For example, light blue indicates that a voxel is disconnected to 75% to 100% of the voxels in the corresponding cluster.

3. Results

- Fig. 5 shows the connectivity indices of the 17 aMCI and 22 CN subjects.

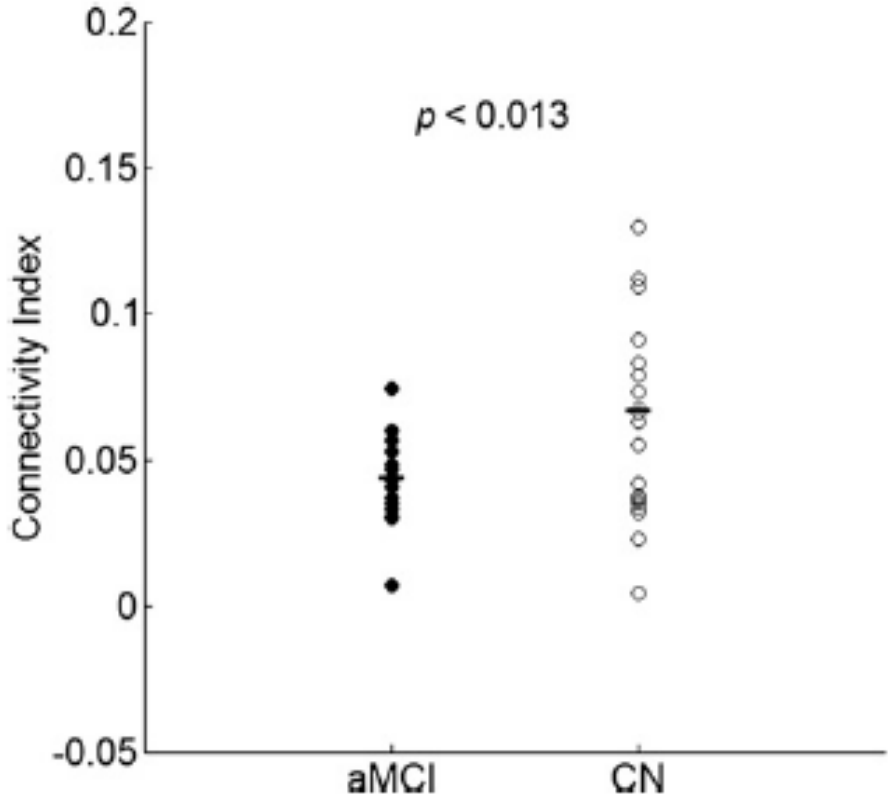


Fig. 5. Connectivity index calculated using the leave-one-out procedure. The connectivity indices of the aMCI group are significantly lower than those of the CN group ($p<0.013$).

4. Discussion

- We introduced a new clustering-based method that can clearly define the **reference clusters.**

- Clusters with homogeneous functional **connectivity changes** between the aMCI and CN groups were identified.

- The method may be **generalized** to multiple groups to detect functional connectivity differences among subjects with Alzheimer's disease, aMCI and CN status.

5. Limitations

- **Increase** the computation cost comparing with ICA.
- The method may only be sensitive to **pairwise-type** correlations.
- The connectivity differences may be **too small to be detected** at this level. They may be more discernible if one uses the full multivariate information, as in the case with the ICA.

6. Conclusions

- The distribution of the reference clusters, as well as their disconnected regions, resembled the **altered memory network regions** identified in task-fMRI studies.

- The connectivity indices obtained from the leave-one-out analysis were **significantly different** between aMCI and CN subjects.

- The method has the potential to identify **brain connectivity biomarkers**, which can be used to classify disease status, predict individual behavioral performance, and monitor the efficacy of disease-modifying therapies.